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## Studies on the Development of Inflammatory Lesions

### I. Influences of Cortisone and Methylandrostendiol on Experimental Tuberculosis

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#### Introduction

Susceptibility to tubercle bacilli is considered to be different in each individual. This difference seems to be due to the degree of the native resistance for tubercle bacilli. As well known, there is also a difference between the races, for instance, albino rats have greater host resistance for tuberculosis than guinea pigs. Variability of those resistance by some definite conditions seem to be especially interesting. Lately, some facts regarding this have become known.

Natural resistance for infection is decreased by administration of cortisone. Clinical observations have also revealed that the administration of cortisone or adrenocorticotrophic hormone to patients with pulmonary tuberculosis might develop a miliary dissemination. Michael et al<sup>1)</sup> have produced the overwhelming tuberculosis in the albino rats, normally a highly resistant animal, through the daily injections of cortisone for a prolonged period. The same enhancement of the progress of tuberculosis in cortisone treated mice and guinea pigs was found by Hart<sup>2)</sup> and Spain<sup>3)</sup>.

From the above facts, one may postulate that the native resistance for tuberculosis, to some extent, is dependent on hormones.

Even in the tuberculous lesions which were produced by the same strain of tubercle bacilli, the findings may be irregular. Takamatsu<sup>4)</sup> has designated them as three fundamental types of tuberculous lesions, namely exudative, proliferative and productive types. These three types of changes were determined by the stage of infection and by endogenous factors such as hormones and constitution. Nakamura<sup>5)</sup> emphasized nutrition as one of the factors. Depression of the inflammatory response following the administration of cor-

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tisone was reported by many authors (Dangherty<sup>6</sup>), Michael et al<sup>11</sup>). Germuth and Ottiuger<sup>7</sup>) have elicited that cortisone diminished markedly antibody formation.

Since the theory of general adaptation syndrom was mentioned by Selye<sup>8</sup>), the hormonal influence on the inflammation as the local defence reaction has come to be examined. From the point of view of inflammation, adrenocortical hormones were divided into two groups, antiphlogistic and prophlogistic (Selye)<sup>8</sup>). The influence of various hormones upon formation and structure of mesenchymal tissues has aroused considerable interest, since the importance of these tissues in defense and disease mechanism was recognized. Many experimental results were reported about the influence of various steroid hormones on the inflammation and granulation (Lipschutz<sup>9</sup>), Taubenhaus<sup>10</sup> 11).

Table 1

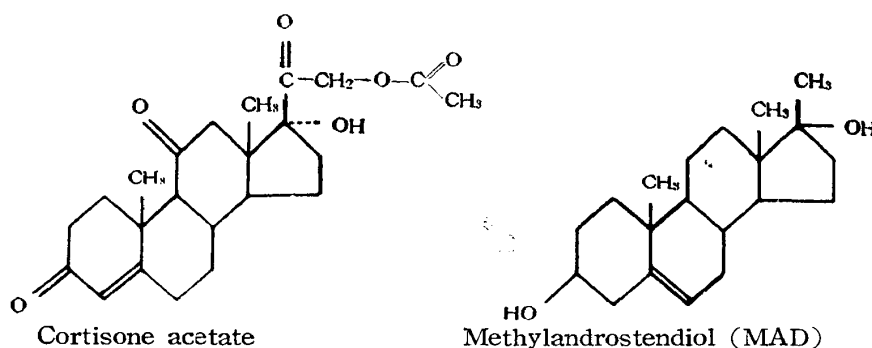


Table 2

	mg/ daily	Number of animals (Experimental period)			
		Fifth week	Seventh week	Tenth week	Twentieth week
Tuberculous control group		4	3	2	
Cortisone treated group	3.0 mg/kg	4	3	2	
MAD treated group	1.5 mg/kg	4	3	3	2

The author has attempted, hitherto, to assay each factor of fundamental phenomena of inflammation. The varieties of the development of those fundamental phenomena will cause many types of lesions. So, if we find any chemicals having such governing effects on the pattern of lesions, some contributions should be expected on pathogenetic study and also in practice. For this reason, the current views on the influences of hormones attracted the author and then the administration of hormones was adopted in the plan of the analytical studies in the course of tuberculous and non-

tuberculous inflammation.

The influence of some steroid hormones on tuberculous lesions was examined at first. The effects of cortisone and methylandrostendiol (MAD) are especially interesting (Table 1). Above all, the peculiar effect of MAD on the tuberculous lesions was found for the first time in our laboratory and the results were made public at the 6th annual meeting of the Japanese Association for Constitutional Medicine (1955) and the 31st annual meeting of the Japanese Association for Tuberculosis (1956).

In this paper, as the first report of this series, the author will discuss his own experiments concerning cortisone and MAD.

### **Materials and Methods**

Thirty male guinea pigs weighing 400 to 500 gm were used for this experiment. The first group was injected with 0.1mg of H<sub>37</sub>Rv (virulent human tubercle bacilli) in each thigh, the second group was injected likewise with 0.1 mg of H<sub>37</sub>Rv, and three weeks later with the daily dose of 3.0mg/kg cortisone acetate (Merck) was introduced intramuscularly for the various periods as shown in table 2. The third group was injected with 0.1 mg of H<sub>37</sub>Rv, and three weeks later, 1.5mg/kg of Methylandrostendiol (Megabion-Teikokuzoki) was injected as the daily dose, for the various periods shown in the table 2.

At autopsy, gross findings and distribution of tuberculous lesions were examined. Histologically, the lung, liver, spleen and lymphnodes were studied with hematoxylineosin and also Van Gieson's stain.

### **Experimental Results**

Body weight of the animals :

Half of the animals which were administrated with cortisone acetate died within three weeks. An average weight of the infected guinea pigs of cortisone group decreased about 50 gm at the end of this period, whereas that of the animals which had been treated with MAD increased about 20 gm. The control group of tuberculosis showed no changes in weight.

#### **1. The findings of control group of guinea pigs by infection.**

##### **a) Lung**

At the fifth week, no lesions were found macroscopically. And in this period no typical tubercles were observed histologically.

At the seventh week, small, mostly subpleural foci of granulomatous pneumonia were observed. The inflammatory findings consisted chiefly of

large mononuclear cells of the epithelioid cell type. Lymphocytes were encountered in fair numbers and the process had elicited no fibroblastic response. There was no caseation in the foci.

At the tenth week, many minute granulomata consisting of mononuclear cells were seen. The granulomate consisted chiefly of epithelioid cells, large vacuolated macrophages and a few multinucleated cells of the Langhans' type in the central portion of the foci. Many lymphocytes were encountered in the periphery, and some fibroblastic responses were found. In some of the epithelioid cells and multinucleated cells, vacuolated changes were observed.

#### b) Liver

In the fifth week, relatively many minute granulomata consisting of mononuclear cells were seen in the liver. The lesions were found chiefly in portal and periportal areas. No or minute lymphocytic infiltration was observed around the foci, so the granulomata seemed to be adjacent to liver cells. There was no caseation.

In the seventh week, many liver cells became atrophic, and dissociation of the cells was observed. Typical tuberculous granulomata were found chiefly in portal and periportal areas. Necrosis was found in large granulomata, but not in small ones. The inflammatory foci were occupied chiefly by large mononuclear cells of the epithelioid cells. Few lymphocytes were found but no Langhans giant cells were noticed. In large granulomata vacuolated epithelioid cells existed. Few or no fibroblastic response had elicited and proliferation of small bile duct was found to some extent.

In the tenth week, many tuberculous granulomata consisted with epithelioid cells were seen in the liver. The liver cells of the many cases showed in atrophic pattern but in some of other cases, on the contrary, a hypertrophy was shown, and a large amount of bile pigments were observed in the atrophic liver cells. Tuberculous granulomata became relatively large in size and vacuolated epithelioid cells and Langhans giant cells were observed there.

#### c) Spleen

In the fifth week, a few minute granulomata similar to those in the liver were seen scattered throughout the spleen. The necrosis existed in the central portion of the foci. The inflammatory process consisted chiefly of large epithelioid cells and lymphocytes. No fibroblastic response was observed.

In the seventh week, many tuberculous granulomata were observed some of which were confluent. Necrosis and cell break down were found in the central portion of the foci. Many lymphocytes infiltrated in the

granulomata.

In the tenth week, most portions of the spleen were occupied by tuberculous foci. Conflux of granulomata was also found. Central caseation was seen in the large granulomata and vacuolated epithelioid cells existed. Langhans giant cells and foreign-body giant cells were also found. In some parts, epithelioid cells arranged in arc form, and this finding seemed to suggest the genesis of Langhans type of giant cells. In some degree, fibroblastic reactions existed in the periphery of the granulomata.

#### d) Lymphnodes

In the fifth week, central necrosis and cell break down were observed in the swollen regional lymphnodes, and connective tissues of the capsula were proliferated markedly. In other lymphnodes, central necrosis and infiltration of lymphocytes in the peripheral portion of the granulomata were also observed. The lesions were composed chiefly with the formation of epithelioid cells and Langhans giant cells. No or few fibroblastic responses were observed.

In the seventh week, the confluence of the foci was observed. Central portion of this foci was necrotic and many epithelioid cells and lymphocytes were observed. Fibroblastic response was slightly observed.

In the tenth week, most of the foci were confluated and central necrosis still existed. Many vacuolated epithelioid cells were scattered in the granulomata. A few degenerative Langhans giant cells were also found. In the small granulomata, vacuolated changes were not observed in epithelioid cells and the membrane of this cell was not distinct. The fibroblastic response was slightly observed.

## 2. The findings of the group administrated with cortisone.

#### a) Lung

In the lungs of the infected guinea pigs which were administrated with cortisone, the lesions were seen as diffuse and wide spread foci or caseous pneumonia in general. In the fifth week, these lesions consisted chiefly of large mononuclear cells with a foamy cytoplasm but the typical epithelioid cells and lymphocytes were comparatively few in number and no fibroblastic proliferation was present.

In the seventh week, the widespread, diffuse tuberculous granulomata were observed as shown in the fifth week. Large necrosis existed in the central portion of the foci. A few epithelioid cells and lymphocytes were

noted, and fibroblastic proliferation was not present.

b) Liver

In the fifth week, many tuberculous granulomata consisting of mononuclear cells were seen in the liver. The lesions were found in portal and periportal areas, as seen in control animals. There was a large caseation in the central portion of tubercle. Degenerative changes, such as pyknosis and vaculation were seen in epithelioid cells. A few multinucleated Langhans cells were found. In some of them nuclear break-down was observed. Minute or no lymphocytic infiltration was noted, and no fibroblastic proliferation was present.

In the seventh week, the histological finding was similar to that of fifth week. Large necrosis was found in the central portion of the foci. Most of the tubercles were confluent in this period. Bile duct proliferation was not as prominent as in control group. Degenerative changes were seen in epithelioid cells and Langhans giant cells. Lymphocytic infiltration and fibroblastic proliferation were scarcely observed.

c) Spleen.

In the fifth week, numerous minute granulomata similar to those in the liver were scattered throughout the spleen. There was a marked lymphoid depletion and granulation composed predominantly of epithelioid cells. The lesions lacked peripheral cellular response. Much central necrosis was also seen in granulomata.

In the seventh week, large necrosis was observed in the granulomata. Many vacuolated epithelioid cells were seen. Peripheral lymphocytic response and fibroblastic response were not observed with other organs.

d) Lymphnode

The tuberculous changes in the lymphnodes were almost similar to those of spleen.

3. The findings of the group administrated with MAD.

a) Lung.

In the fifth week, a few small tubercle were seen in the lung. The inflammatory process consisted chiefly of epithelioid cells and lymphocytes.

In the seventh week, the granulation was occupied with epithelioid cells and there was no caseation in the central portion of the granulomata. Peripheral fibroblastic response was slightly apparent in these animals.

In the tenth week, peripheral fibroblastic response was relatively strong

and the tuberculous lesion was of productive type.

In the twentieth week, a few caseations existed. The inflammatory process consisted of proliferated epithelioid cells. Vacuolation and pyknosis were found in these epithelioid cells. Small numbers of lymphocytes were elicited around the granulation. A collagenous fiber encapsulated these granulomata.

#### b) Liver

In the fifth week, the tuberculous granulomata were found chiefly in portal and periportal areas. The inflammatory process consisted chiefly of proliferated epithelioid cells and lymphocytes. There was no caseation in the central portion of the granulomata. Fibroblastic response was found around the granulomata and among the epithelioid cells. Small bile ducts also proliferated in the neighboring tissue around the granulomata. These proliferated epithelial cells of the small bile ducts resembled the epithelioid cells. But these cells had a distinct nucleolus and the cells were smaller than epithelioid cells. Central necrosis consisted in the large granulomata, but there was no necrosis in the small granulomata. By Van Gieson's stain, thick collagenous fiber layer encapsulated these granulomata and were found among the epithelioid cells. From this histological finding, MAD seemed to hasten the inflammatory process to productive type.

In the seventh week, the liver cells were generally atrophic and the inflammatory process consisted chiefly of proliferated epithelioid cells. Marked lymphocytic response was found. Langhans giant cells were not observed. Fibroblastic response was strong. A small bile duct was also proliferated to a remarkable degree.

In the tenth week, the liver was enlarged to three or four times that of the control animals and showed hypertrophic liver cirrhosis. Liver cells showed remarkable atrophy and the liver was occupied by proliferated epithelium of small bile duct. Many liver cells showed fatty degeneration. Some of them contained yellowish bile pigment. Irregular lobes and diffuse necrosis of liver cells were found. Minute granulomata existed in the proliferated bile ducts. In some portion proliferation of the large bile ducts were seen. The inflammatory process consisted chiefly of large epithelioid cells, which had no vacuolated changes. Around these epithelioid cells, lymphocytic and fibroblastic response were found. And among epithelioid cells, collagenous fibers were found. In some granulomata, hyalination of the central portion and disappearance of epithelioid cells were observed.

In the twentieth week, the liver was tremendously enlarged up to four or five times the normal size of the liver. Large hemorrhagic infarct was



seen. Microscopically, the liver cells were scarcely found and the liver was occupied almost by proliferated small bile ducts. The inflammatory process consisted of large epithelioid cells, and neither caseation nor necrosis were found. Hyalination existed in the granulomata.

### c) Spleen

In the fifth week, many granulomata were found throughout the spleen. The inflammatory process consisted chiefly of proliferated large epithelioid cells. Mitotic figures of epithelioid cells were found. No caseation was observed. Giant cells with the arc-like arrangement of the nuclei were found in the peripheral portion of the granulomata. Lymphocytic response was found to some extent. In large granulomata, central necrosis was observed, and vacuolated and pyknotic epithelioid cells were also observed. By Van Gieson's stain, abundant collagenous fibers encapsulated the granulomata and existed among the epithelioid cells.

In the seventh week, granulomata were similar to those of the fifth week group. Central caseation was observed in every granulomata. Fibroblastic response had increased over that of the fifth week.

In the tenth week, atrophy and congestion were more marked and hemorrhagic infarcts were observed. Cirrhotic changes were observed in tuberculous lesions, and hyalination was common in the central part of the granulomata. Much fibroblastic response was observed. Epithelioid cells showed vacuolation. In the granulomata caseation was scarcely present. A few Langhans giant cells existed, but they had vacuolation.

In the twentieth week, large granulomata was observed. In some of the large granulomata, central caseation was found. Hyalination was common in the central areas of the granulomata. Many round crevices were observed in the periphery of the caseation. Degenerated epithelioid cells and giant cells were found. Fibroblastic response was much greater.

### b) Lymphonodes

In the fifth week, in the hilus of the lung, central caseation, proliferated epithelioid cells and lymphocytic response were observed. Vacuolation was seen in the epithelioid cells and Langhans giant cells. The encapsulating fibroblastic layer was thick and diffuse.

In the seventh through the tenth week, the fibroblastic response had increased and productive changes were observed. Many degenerated epithelioid cells and Langhans giant cells were scattered in the granulomata.

In the twentieth week, the changes of the granulomata were similar to those of the tenth week, the fibroblastic response was much more marked

and lymphoid depletion was also observed.

### Discussion

The influences of hormones on inflammation, especially of cortisone and adrenocorticotrophic hormone (ACTH) have been widely examined. Taubenhau<sup>10)</sup> showed certain hormones influenced qualitatively and quantitatively the granulation tissue around the abscess induced on rats by turpentine injections. Lipschutz examined the antifibromatogenic action of various steroids.

The effects of cortisone on inflammation are merely upon the side of body reaction and not on the exogenous bacilli. Ozawa and Botaiji<sup>12)</sup> reported that cortisone has no effect on tubercle bacilli. William<sup>13)</sup> described the same results in his experiments in vitro. The fibroblastic response and encapsulation of the foci were depressed by cortisone, resulting in the retardation of healing of the infected wound. Gicatrization of wound was inhibited by cortisone (Ragan<sup>14)</sup>, Plotz<sup>15)</sup>, Banghan<sup>16)</sup>). The ability of inhibiting the proliferation of mesenchyma was observed by injection of cortisone (Ingle<sup>17)</sup>, Lipschutz<sup>9)</sup>).

The effects of adrenocortical hormones are twofold ; that of cortisone inhibiting fibroblast and collagen formation and that of desoxycorticosterone acetate (DOCA) stimulating fibroblastic response. Taubenhau<sup>10)</sup> and Takada<sup>18)</sup> reported that DOCA stimulated the proliferation of fibroblasts and the depletion of the homogenous diffuse ground work of collagen. And still more remarkable effects were obtained by the combined use of DOCA and ascorbic acid (Miyata<sup>19)</sup>).

The mechanism of DOCA on the connective tissue has not been clearly elucidated. Taubenhau, however, reported that water and salt metabolism was affected by DOCA and this electrolytic changes might produce fibroblastic response. The author observed in tuberculous guinea pigs, the same fibroblastic response of MAD with DOCA.

MAD is a kind of androgen. The protein anabolic effects of androgen has been demonstrated by many authors (Kenyon<sup>20)</sup>, Howard<sup>21)</sup>, Albright<sup>22)</sup>, Reifenstein<sup>23)</sup>). Thess effects consist in the synthesis of protoplasm, and in the retention of nitrogen, phosphorus and potassium. Cohen<sup>24)</sup> showed the weight gains were strikingly great in the patients who received testosterone propionate in comparison with that of the controls. And the author observed the same result in the tuberculous guinea pigs which received of MAD.

Anabolic action of MAD is much more effective than that of testosterone propionnate, and connective tissue proliferation in tuberculous lesions might be due to this action. In another experiment of the author, the effects of

testosterone propionate were not strikingly greater on tuberculous guinea pigs than that of the group treated with MAD.

The fibroblastic response caused by MAD was limited to the infected foci and MAD seemed to promote the local defense reaction of the injured foci. Higashimori<sup>25)</sup> demonstrated that MAD accelerated the adrenocortical regeneration of the adrenal in enucleated animals. MAD stimulates therefore not only the response against infectious agents, but promotes the defense reaction and tissue regeneration in the injured foci.

Of special interest were the changes in the liver of tuberculous guinea pigs treated with MAD. In tuberculous guinea pigs, the remarkable proliferation of pseudo bile ducts was denoted by many investigators from the seventh to the twentieth week of infection (Aoki and other authors<sup>26)</sup>). This change agrees somewhat with tuberculous liver cirrhosis or hepatic fibrosis. In this experiment, we also observed a proliferation of small bile ducts in tuberculous guinea pigs. But by MAD administration to tuberculous guinea pigs, the proliferation of small bile ducts and fibrosis became especially severe, and proliferated small bile ducts occupied most parts of the liver.

This proliferation of small bile ducts sometimes appeared so overwhelmingly that the other reaction became obscure. In contrast, the proliferation of bile ducts in the cortisone treated animals was scarcely observed. According to Aterman<sup>27)</sup> and Cavello<sup>28)</sup>, the hepatic fibrosis which was caused by  $\text{CCl}_4$  was also inhibited by cortisone.

Therefore the author may safely conclude that the tuberculous foci will be greatly modified by the actions of some hormones, and to some extent, hormonal activities of the body may contribute to the individual differences in susceptibility to tuberculosis.

### Summary

In this paper, the author observed the influences of various steroid hormones on tuberculous lesions as a part of the study in the general tissue reaction. Thirty guinea pigs were infected and then administered with several hormones at the 3rd week after the inoculation. At the various periods (the 5th, the 7th, the 10th and 20th week after the infection), the macroscopic and histological findings of the lesions were investigated. The following results were obtained; by the administration of cortisone or MAD (Methylandrostendiol), the patterns of the tuberculous lesions were greatly modified. Multiplication of fibroblasts and infiltration of lymphocytes were inhibited by the administration of cortisone in this experiment. On the other hand, fibroblastic response and proliferation of epithelioid cells were promoted by the administration of MAD according to

its periods. Therefore MAD seems to hasten inflammatory process to the productive type.

Due to the administration of MAD, a proliferation of small bile ducts of the tuberculous animals was also observed.

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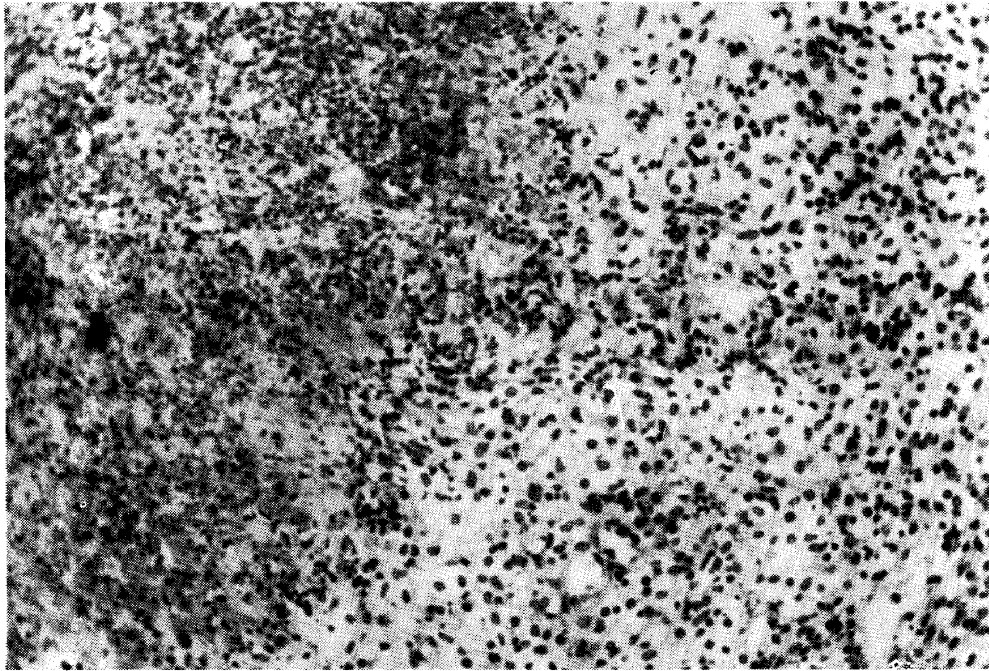


Fig. 1 Cortisone administered group ; A lesion in the spleen, in the fifth week of the experiment. Central necrobiosis is widely spread in the area. (× 200)

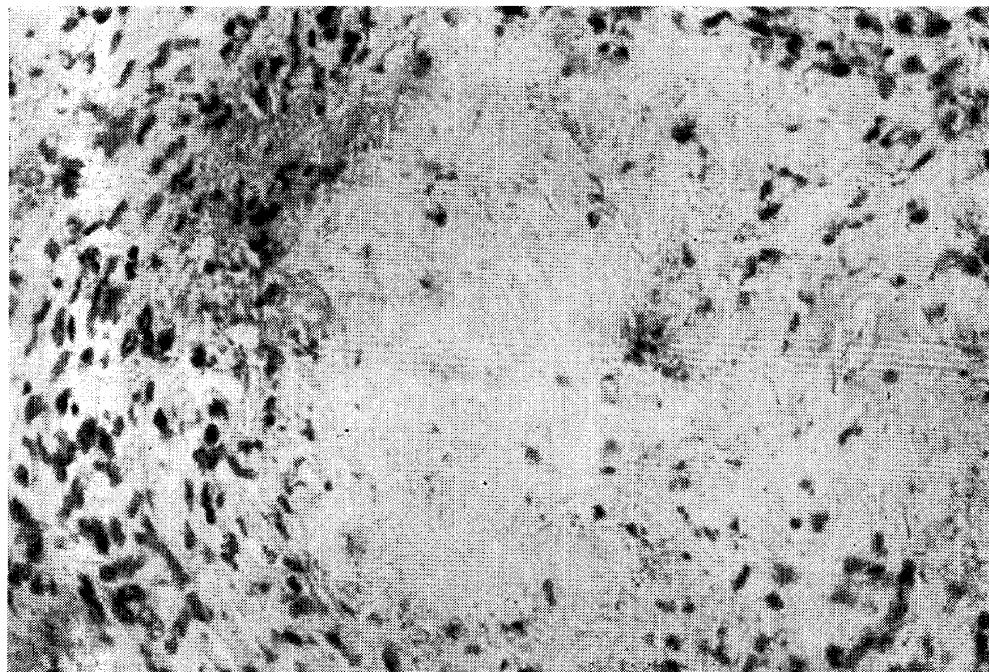


Fig. 2 Cortisone administered group ; A lesion in the liver, in the seventh week of the experiment. Caseation is observed in the granulomata and fibroblast formation is hardly observed. (× 400)

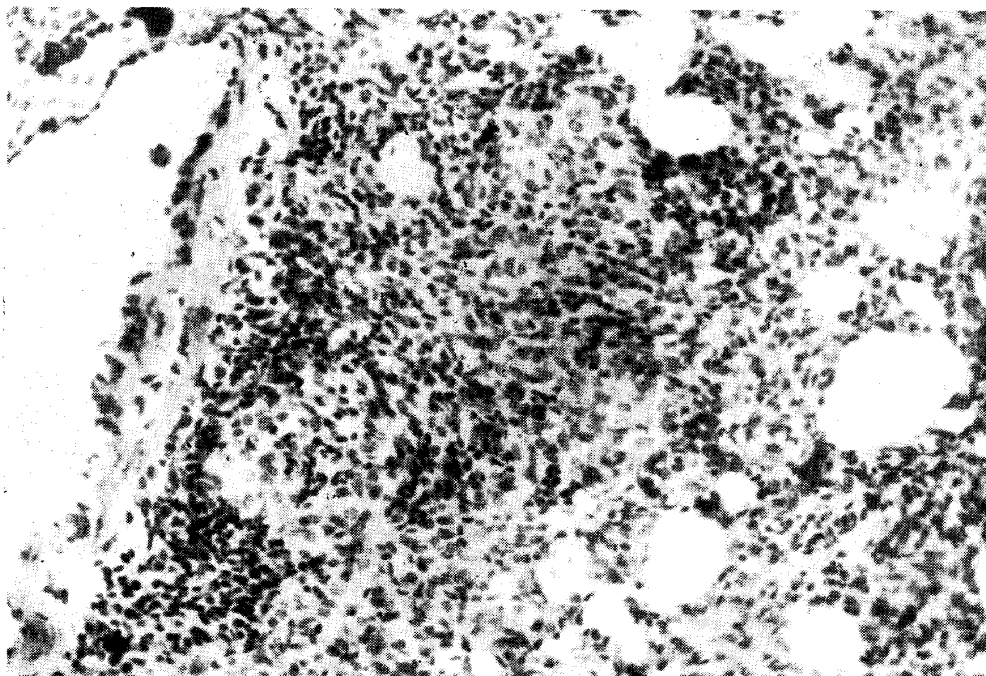


Fig. 3 MAD administered group ; A lesion in the lung, in the tenth week of the experiment. The granulomata consist chiefly of epithelioid cells and many lymphocytes are encountered in the periphery. The fibroblastic response is intensified to some extent. ( $\times 200$ )

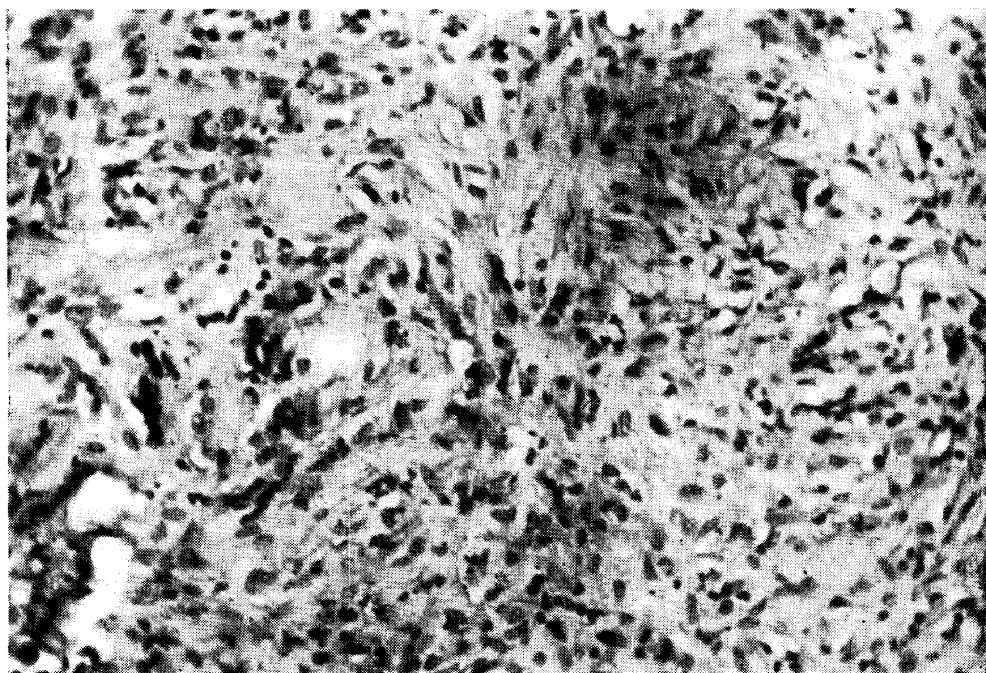


Fig. 4 MAD administered group ; A lesion in the lymphnode, in the tenth week of the experiment. Increase of fibroblast and new fiber formation are noticeable. ( $\times 400$ )



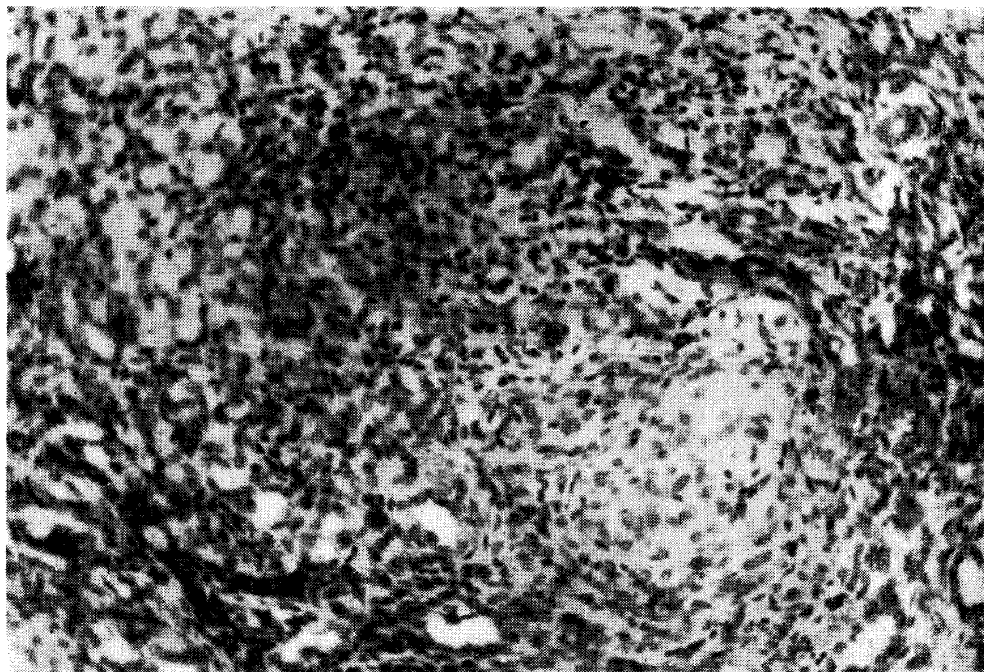


Fig. 5 MAD administered group. A lesion in the liver, at the tenth week of the experiment. The liver is occupied by the proliferated epithelium of small bile duct. Combined with these ducts, large epithelioid cells and collagenous fibers are constituted in the area. ( $\times 200$ )

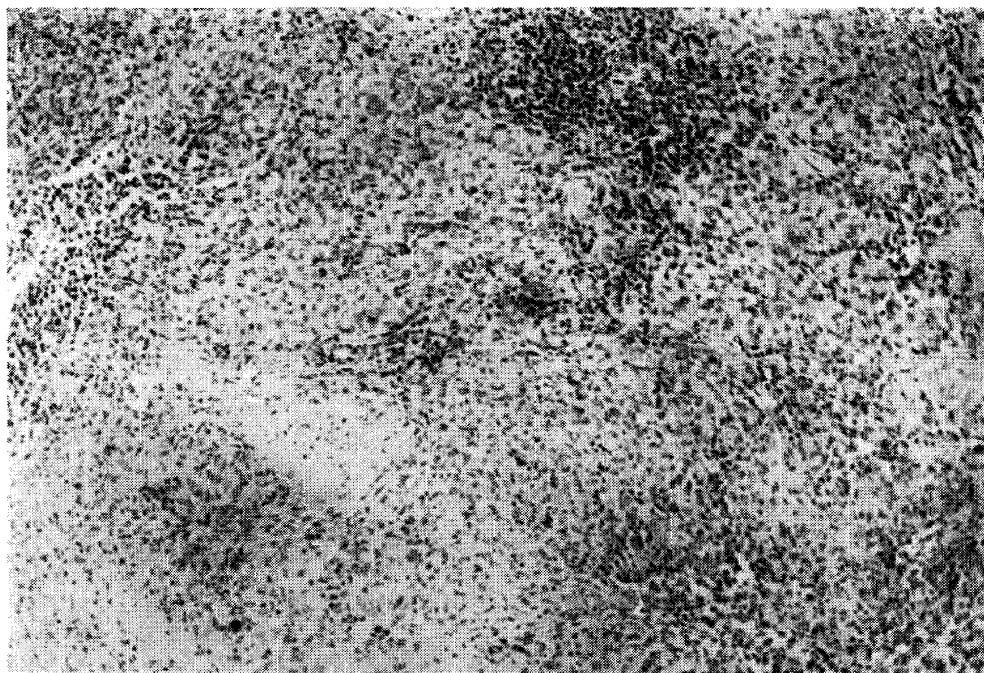


Fig. 6 MAD administered group. A lesion in the liver, at the twentieth week of the experiment. The liver cells are scarcely found in this sites and it is occupied mostly by proliferated small bile ducts. Hyalinization exists in the granulomata. ( $\times 100$ )